## *Remarks*

Reconsideration of this Application is respectfully requested. Applicants respectfully request the entry of this Amendment and Reply after a final Office Action because the amendments place the claims in better form for consideration on appeal and in condition for allowance. *See* 37 C.F.R. § 1.116(b).

Upon entry of the foregoing amendments, claims 166, 168, 170, 177 and 247-252 are pending in the application, with claims 166 and 248 being the independent claims. New claims 248-252 are sought to be added to include claims directed to the elected peptide that correspond to claims 166, 168, 170, 177 and 247. As such, new claims 248-252 fall within the scope of the elected invention and are believed to introduce no new matter.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejection.

### *Rejection Under 35 U.S.C. § 103*

Claims 166, 168, 170, 177 and 247 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chien, in view of Berzofsky *et al.* (U.S. Patent No. 5,980,899) and Guo *et al.* (*Nature 360*:364-366 (1992)). Applicants traverse the rejection.

#### *Legal Principles*

The standard for obviousness is set forth in 35 U.S.C. § 103 as follows:

> A patent may not be obtained though the invention is not identically disclosed as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as

> a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. § 103(a) (2000).

The United States Supreme Court addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727 (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) factors provide a framework to make a determination of obviousness. Those factors are: (1) "the scope and content of the prior art"; (2) the "differences between the prior art and the claims"; (3) "the level of ordinary skill in the pertinent art"; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734 (*quoting Graham*, 383 U.S. at 17-18).

The Supreme Court has recently stated that "[w]hen there is a design need or market pressure to solve a problem and there are a *finite number* of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. . . . [i]n that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *See KSR* at 17 (emphasis added).

> ***The cited references do not render the claims obvious because the cited references, at best, provide an extremely large number of epitopes from which screening criteria cannot guarantee the selection of an immunogenic CTL epitope.***

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (Fed. Cir. 2007), a post-*KSR* case, the Federal Circuit elaborated on the issue of obviousness where the prior art disclosed a large number of possible solutions. In its analysis, the Federal Circuit stated that:

> Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. . . . Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

*Takeda*, 492 F.3d at 1359. Applicants maintain that the present case is similar to the situation in *Takeda*. In this instance, the cited references, at best, provide an extremely large number of epitopes upon which one of ordinary skill in the art can apply certain screening criteria, where the screening criteria provide no guarantee that an immunogenic CTL epitope will in fact be identified.

Applicants note that Chien discloses over 180 different HCV fragments ranging in size up to 70 amino acids in length, and spanning a sequence that is nearly 3000 amino acids in length. Chien does not indicate whether any particular fragments are preferable to any others. Chien merely divides the larger approximately 3000 amino acid sequence into various smaller fragments. There are potentially hundreds of different immunogenic epitopes that could be selected within the larger approximately 3000 amino acid sequence, and within all of the various smaller fragments. If one were guided to one particular fragment of the hundreds listed, one would be provided with a smaller source of potential CTL epitopes. However, this is not what Chien provides. Chien does not provide any guidance as to which particular fragment would be best suited to obtain an immunogenic HCV sequence. In fact, Chien states that:

> [i]t is to be understood that these peptides do not necessarily precisely map one epitope, but may also contain HCV sequence that is not immunogenic.

Chien at col. 27, lines 10-13.

Furthermore, Chien, in discussing ways that one of ordinary skill in the art could apply techniques to identify potential immunogenic candidates, also notes that:

> [i]t is appreciated by those of skill in the art that such computer analysis of antigenicity does not always identify an epitope that actually exists, and can also incorrectly identify a region of the protein as containing an epitope.

Chien at col. 27, lines 4-8. Thus, Chien provides about 3000 amino acids of sequence from which an immunogenic peptide could be derived, but using the disclosure of Chien, it would not be at all predictable to arrive at Applicants' claimed peptide.

While the Examiner may hone in on a particular fragment (AA1850-AA1900) using Applicants' claimed peptide as a starting point, this is applying hindsight reasoning in selecting which particular fragment, of the hundreds disclosed in Chien, to use as a starting point. Applicants maintain that there is nothing in Chien that points to the AA1850-AA1900 fragment in particular, and without the knowledge of Applicants' claimed peptide being a CTL epitope, nothing in Chien would lead to Applicants' elected peptide, let alone the AA1850-AA1900 fragment that *comprises* the peptide.

In *Takeda*, the Federal Circuit distinguished the facts of the case from those in another of their recently-decided cases, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). The Federal Circuit stated that in *Pfizer*, in contrast to *Takeda*, the "prior art provided 'ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.' Here, the court found nothing in the prior art to narrow the possibilities of the lead compound to compound b." *Id.*

In the present case, none of the references cited by the Examiner provide the guidance as presented in *Pfizer* that would allow one of ordinary skill in the art to further

narrow down the large number of possible HCV CTL epitopes that could be obtained. Applicants maintain that it would have been unpredictable, in view of the cited art, to arrive at Applicants' claimed peptide. This proposition is further supported by the Declaration of Dr. Alessandro Sette (*i.e.*, one of ordinary skill in the relevant art), filed as Exhibit E of the Amendment and Reply filed on September 25, 2009 ("Sette Declaration"). In particular, it is Dr. Sette's opinion that:

> one of ordinary skill in the art, considering the art related to CTL peptides motifs as a whole, would not be able narrow down the huge number of equally reasonable HCV CTL epitope candidates to a more finite number of identifiable, predictable solutions.

Sette Declaration at ¶ 36; *see also* Sette Declaration at ¶¶ 37-39.

Thus, in view of *KSR* and the subsequent decisions of *Takeda* and *Pfizer*, the present invention is not rendered obvious by Chien in view of Berzofsky or Guo.

***The Examiner has not addressed the evidence presented in Dr. Sette's Declaration regarding the scope and content of the prior art, the differences between the prior art and the claims, and the unexpected results of the present invention.***

As evidence of the scope and content of the prior art, the differences between the prior art and the claims, and unexpected results of the present invention, Applicants wish to remind the Examiner of the Sette Declaration. Applicants note that the Examiner has not addressed many of the arguments and evidence presented in the Sette Declaration. For example, the Examiner has not addressed the facts set out in paragraph 40 of the Sette Declaration (*i.e.*, that the elected peptide exhibits one of the highest binding affinities and immunogenicities of the over 400 other peptides sharing the same A3 motif). As such, Applicants maintain that one of ordinary skill in the art would not have expected that *this particular peptide* would have had higher affinity and immunogenicity

that the others sharing the same A3 motif. This criticality of the HLA binding affinity is also disclosed in the specification, for example, at paragraphs [0096]-[0097].

Chien discloses the sequence of the HCV genome which is about 3000 amino acids in length. In columns 27-28, as noted in the Sette Declaration, Chien lists a series of overlapping amino acid fragments arbitrarily generated and spanning the entire HCV genome. *See* Sette Declaration at ¶¶ 12-13. The AA1850-AA1900 fragment, referenced by the Examiner in the Office Action, is only one of the 188 fragments listed in columns 27-28. *See* Sette Declaration at ¶ 12. Each of these 188 fragments varies in size, from approximately 5 to 265 amino acids in length. Chien does not indicate whether any of the 188 individual fragments are preferable to any others.

Moreover, Chien does not provide any guidance as to which particular fragment would be best suited to obtain an immunogenic HCV sequence. Looking at Chien, each of the 188 fragments would be an equally reasonable alternative with which to start in the process of selecting an antigenic peptide. In fact, Chien states that "[i]t is to be understood that these peptides do not necessarily precisely map one epitope, but may also contain HCV sequence that is not immunogenic." Chien at col. 27, lines 10-13. Furthermore, Chien, in discussing ways that one of ordinary skill in the art could apply techniques to identify potential immunogenic candidates, also notes that "[i]t is appreciated by those of skill in the art that such computer analysis of antigenicity does not always identify an epitope that actually exists, and can also incorrectly identify a region of the protein as containing an epitope." *Id.* at lines 4-8. Thus, as stated by Dr. Sette, Chien offers no further suggestion as to how to narrow down hundreds or even thousands of possible peptides that could be generated by this brute force method to

arrive at one, or even a reasonable number, of possible immunogenic peptides. *See* Sette Declaration at ¶ 15. If one of ordinary skill in the art would look to Chien to identify an immunogenic peptide, he or she would find potentially hundreds or even thousands of different immunogenic epitopes that could be selected within all of the various fragments of the larger ~3000 amino acid sequence.

***The evidence of record is sufficient to show the criticality of the claimed peptide lengths.***

At page 9 of the Office Action, the Examiner argues that:

> the specification discloses that the peptide can be 30 amino acids long and conjugated to a HTL, indicating that according to the teachings of the specification, there is no criticality regarding the length of the peptide.

Applicants respectfully disagree. According to the specification, longer peptides may not be processed in the same manner as, and may contain motifs leading to unwanted side-reactions to, the specific isolated peptides of the invention. *See, e.g.*, paragraphs [0040] and [0042].

To establish unexpected results over a claimed range, test results both inside and outside the claimed range should be compared to show the criticality of the claimed range. *See* M.P.E.P. § 716.02(d) and *In re Hill*, 284 F.2d 955 (CCPA 1960). Such test results are available in the specification. For example, the specification provides that the removal of the N-terminal G-residue of the elected peptide significantly lowered the immunogenicity of the peptide in a transgenic mouse model (*see, e.g.*, Table XXIII of the specification). The comparison of these results for peptides inside (the elected peptide) and outside (the elected peptide with the N-terminal G residue removed) of the claimed range is sufficient to show criticality of the claimed peptides. Also, Applicants

note that claims 166 and 248 are directed to specified *isolated* peptides (*i.e.*, peptides isolated from native surrounding HCV sequences), and that claims 168 and 249 are directed to the subgroup of peptides that are 10 amino acids in length. For at least these reasons, Applicants assert that the evidence of unexpected results of record is sufficient to show the criticality of the claimed peptide lengths, particularly for the peptides claims 168 and 249.

***The Examiner has not provided sufficient evidence to support the propositions that any intact immunogenic molecule would necessarily contain a helper cell epitope, or that the functional attributes of claim 166 would necessarily be present in the peptides disclosed in Chien.***

Chien, as discussed above, does not disclose every element of Applicants' claimed invention. This is supported by the Examiner's own statement that "Chien et al. do not teach the peptide of claim 166/168." Office Action at page 3. The Examiner further states that "[v]irtually any intact immunogenic molecule will contain at least one helper cell epitope." Office Action at page 3. The Examiner, however, has not provided any evidence to support this assertion. As noted above, the Chien reference in fact notes that "[i]t is to be understood that these peptides do not necessarily precisely map one epitope, but may also contain HCV sequence that is *not immunogenic*." Chien at col. 27, lines 10-13 (emphasis added).

The Examiner has also alleged that "the functional attributes of claim 166 would presumably be present in the peptide of Chien et al. in that said larger peptide would be processed in vivo to yield the peptide of claim 166." Office Action at page 7. The Examiner also has not provided any evidence to support this particular assertion.

Applicants have cited Yewdell, Eisenlohr and DelVal (Amendment and Reply of November 15, 2005, and Amendment and Reply dated August 29, 2005) in support of

the proposition that it is difficult to identify exactly which specific peptides are capable of inducing an immune response within a given longer sequence. Applicants note that while flanking resides may be able to positively affect the presentation of an immunogenic peptide, Eisenlohr teaches that the addition of flanking residues can also destroy the antigenicity of a particular peptide. *See* Eisenlohr at page 485, first paragraph. Therefore, an epitope embedded within a larger sequence may be processed differently, and thus have different immunogenicity than the same epitope free of flanking or surrounding amino acid residues. In view of Eisenlohr, the Examiner cannot simply assume that any longer fragment that is processed *in vivo* will predictably generate a smaller immunogenic peptide derived from that longer fragment.

The Examiner also states that:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Chen et al. teach an immunogenic HCV peptide containing GVAGALVAFK, whilst Berzofsky et al. teach that it is desirable to identify CTL epitopes found in HCV and Guo et al. teach that CTL recognize viral peptides complexed with MHC and that peptides which bind HLA-Aw68 generally are 9 to 11 amino acids with a V at P2 (position 2) and a K at the c-terminal position.

Office Action at page 3.

While Berzofsky generally describes other regions of HCV, it does not provide any guidance with regard to which specific regions of the HCV genome necessarily contain good targets for CTL, nor does it contain any guidance to identify Applicants' claimed peptide. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)); *see also*

*Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985) ("The well established rule of law is that each prior art reference must be evaluated as an entirety . . . ."). That is, "[t]here is no suggestion to combine . . . if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *see also KSR* at 12 (reaffirming "the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious") (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)).

Applicants' elected peptide, GVAGALVAFK, is neither discussed, nor described in Berzofsky. In addition, the peptides of Applicants' claimed invention are determined using techniques which do not rely on the amphipathicity algorithm of Berzofsky. Berzofsky does not disclose the techniques Applicants utilized to identify candidate CTL epitopes. Therefore, at best, Berzofsky is an invitation to identify a peptide. Given the large number of possible epitopes that could be identified within the HCV genome and the lack of specific guidance in the Berzofsky article, it cannot be viewed to provide a sufficient reason to modify the art to arrive at Applicants' claimed invention. As such, Chien in view of Berzofsky does not render the claims obvious.

The Examiner maintains that Chien, in view of Berzofsky, and further in view of Guo allegedly renders the claims obvious. Guo generally describes how CTL recognize viral peptides complexed with MHC and that these peptides generally are 9 to 11 amino acids in length. *See* Guo at page 364. While Guo discloses peptide sequences from several proteins including ribosomal 60S, human Hsp70, and influenza NP (*see* Guo at Table 1), Guo does not contain any discussion regarding the identification of CTL

epitopes within the HCV genome, nor does Guo disclose Applicants' elected peptide. The Examiner has also alleged that:

> Regarding applicants comments about Guo et al. and 9mer peptides, said comment is made regarding the prior art. It is not a comment regarding the results disclosed by Guo et al. Guo et al. teach that peptides which bind HLA-Aw68 generally are 9 to 11 amino acids with a V at P2 and a K at the c-terminal position.

Office Action at page 5 (parentheticals omitted). Applicants respectfully maintain that even applying the teachings of Guo to Chien, one of ordinary skill in the art would arrive at a large number of possible candidates considering the large number of fragments, and the approximately 3000 amino acid HCV sequence disclosed in Chien. Thus, in view of the cited art, one of ordinary skill in the art would not predictably arrive at Applicants' claimed peptide. Applicants do not disagree with the Examiner's comments above regarding the disclosure in Guo. However, in view of current legal standards, Applicants disagree with the Examiner's contention that such limited disclosure would be sufficient evidence to support a finding of obviousness, because Guo only provides general guidance regarding a group of peptides and therefore does not sufficiently narrow the scope of the Chien reference to render the claims obvious.

***Even if prima facie obviousness were established, evidence of unexpected results exists which would overcome such a rejection.***

Secondary considerations of non-obviousness include unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 694, 148 U.S.P.Q. 459, 467 (1966). The Federal Circuit has recently reaffirmed that the USPTO must in all cases consider any evidence tending to support secondary considerations of non-obviousness. *In re John B. Sullivan and Findlay E. Russell*, 498 F.3d 1345 (Fed. Cir. 2007). As

discussed herein, the Examiner has not established a *prima facie* case of obviousness with respect to the claims. Moreover, the record demonstrates that *prima facie* obviousness, even if it were established, would be negated by the unexpected and superior properties of the claimed subject matter.

Applicants have shown that the elected peptide GVAGALVAFK exhibits the strongest CTL-inducing response in transgenic mice as compared to any of the other peptides listed in Table XXIII and compared to any of the other peptides which share the same A3 motif. Applicants also point out that in Table XVI, Applicants' elected peptide GVAGALVAFK exhibits one of the strongest binding affinities as compared to over 400 other peptides which share the same A3 motif.

Thus, the CTL-inducing and binding characteristics of the GVAGALVAFK peptide, as determined by Applicants, demonstrate that the GVAGALVAFK peptide has unexpected properties. In view of the improved binding properties of the GVAGALVAFK peptide as compared to over 400 other peptides sharing the same motif, and in view of the significantly greater CTL induction generated as compared to other peptides sharing the same motif, Applicants assert that evidence of nonobviousness and/or unexpected advantageous properties is present. These unexpected advantageous properties of the present invention are also noted in the Sette Declaration at ¶ 40. As such, it is the functional characteristic of the peptide, as determined by the Applicants, which renders the peptide to have an unexpected property, and thus renders the peptide non-obvious in view of the prior art.

While the Examiner has cited the M.P.E.P. in stating that the "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known

invention," (Office Action at pages 6-7 citing *In re Wiseman*, 596 F.2d 1019 (CCPA 1979)), Applicants point out that the elected peptide *was not in the prior art*. Thus, Applicants have not merely recognized latent properties in a prior art compound. In fact, Applicants have not only discovered a *novel* peptide -- GVAGALVAFK -- that would have been unpredictable to obtain from the extremely large number of candidates in the art, but have also determined that this peptide exhibits a superior property. Thus, Applicants selecting the novel GVAGALVAFK peptide out of numerous other possible candidates is nonobvious.

For at least the reasons above, Applicants maintain that Chien, in view of Berzofsky and Guo, does not render the claimed invention obvious. Also, even if *prima facie* obviousness were established, evidence of unexpected results exists which would overcome such a rejection. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

## *Conclusion*

The stated ground of rejection has been properly traversed. Applicants therefore respectfully request that the Examiner reconsider the presently outstanding rejection and that it be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding final Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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